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ORIGINAL ARTICLE

Effects of participation in a U.S. trial of newborn genomic sequencing on parents at risk for depression

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Abstract

Much emphasis has been placed on participant's psychological safety within genomic research studies; however, few studies have addressed parental psychological health effects associated with their child's participation in genomic studies, particularly when parents meet the threshold for clinical concern for depression. We aimed to determine if parents' depressive symptoms were associated with their child's participation in a randomized-controlled trial of newborn exome sequencing. Parents completed the Edinburgh Postnatal Depression Scale (EPDS) at baseline, immediately post-disclosure, and 3 months post-disclosure. Mothers and fathers scoring at or above thresholds for clinical concern on the EPDS, 12 and 10, respectively, indicating possible Major Depressive Disorder with Peripartum Onset, were contacted by study staff for mental health screening. Parental concerns identified in follow-up conversations were coded for themes. Forty-five parents had EPDS scores above the clinical threshold at baseline, which decreased by an average of 2.9 points immediately post-disclosure and another 1.1 points 3 months post-disclosure (both $p \leq .014$). For 28 parents, EPDS scores were below the threshold for clinical concern at baseline, increased by an average of 4.7 points into the elevated range immediately post-disclosure, and decreased by 3.8 points at 3 months post-disclosure (both $p < .001$). Nine parents scored above thresholds only at 3 months post-disclosure after increasing an average of 5.7 points from immediately post-disclosure ($p < .001$). Of the 82 parents who scored above the threshold at any time point, 43 (52.4%) were reached and 30 (69.7%) of these 43 parents attributed their elevated scores to parenting stress, balancing work and family responsibilities, and/or child health concerns. Only three parents (7.0%) raised concerns about their participation in the trial, particularly their randomization to the control arm. Elevated scores on the EPDS were typically transient and parents attributed their symptomatology to life stressors in the postpartum period rather than participation in a trial of newborn exome sequencing.

KEYWORDS

exome sequencing, mental health, newborn screening, parents, pediatrics, psychosocial

Clinical Trial: Genomic Sequencing for Childhood Risk and Newborn Illness (NCT02422511).

1 | INTRODUCTION

As genomic sequencing becomes increasingly integrated into clinical practice and research, concerns remain about the potential for secondary findings unrelated to the indication for sequencing to cause psychological harm, including depression and anxiety. Of equal concern are the potential psychological harms of using genomic sequencing to screen for risk of disease in otherwise seemingly healthy individuals, particularly children. Currently, sequencing of healthy individuals is primarily being implemented in research settings (Frankel et al., 2016; Johnston et al., 2018).

Most studies of the return of genomic information in adults show no evidence for psychological harm (Bloss et al., 2011, 2013; Christensen et al., 2016; Green et al., 2009; Hartz et al., 2014; Robinson et al., 2019; Sie et al., 2015; Wasson et al., 2013). However, few studies have examined the impact of newborns' genomic information on parents, a potentially vulnerable population, as these parents are at risk for Major Depressive Disorder with Peripartum Onset (Gray et al., 2014). Moreover, the majority of studies examining the psychological impact of the return of genomic information enroll subjects who do not have a mood disorder (based on pre-screening), and studies rely solely on quantitative assessments. Thus, previous literature provides little insight into psychologically vulnerable populations, or the reasons why some participants have elevated scores on screening measures of depression.

The Genomic Sequencing for Childhood Risk and Newborn Illness study ('The BabySeq Project') directly addresses the potential psychological harms of integrating the return of newborns' genomic sequencing results to parents into newborn screening. The BabySeq Project was one of four projects co-funded by the National Institutes of Child Health and Development (NICHD) and the National Human Genome Research Institute (NHGRI) in the **N**ewborn **S**equencing **I**n **G**enomic Medicine and Public **H**eal**T**h (NSIGHT) consortium aimed to study the ethical, social, and legal implications (ELSI), clinical utility, and economic outcomes of genomic sequencing in newborns (Berg et al., 2017). The goals of this current analysis are to understand why parents in The BabySeq Project had screening depression scores that were above the threshold for clinical concern and to determine whether participating in the trial in which their infant's genomic results were returned contributed to their depressive symptomatology. We also discuss the extent to which safety protocols in genomic research should be included in future studies in comparison to the protocols in the clinical realm.

What is known about this topic

There is a theoretical risk that returning exome sequencing results to parents regarding their children, particularly healthy newborns for which genomic testing is typically not indicated, will cause psychological harm.

What this paper adds to this topic

By including parents whose baseline depression screening score met the threshold for clinical concern and could be considered a vulnerable population, we were able to observe if their elevated scores persisted after return of genomic results. Additionally, our safety intervention of contacting parents if they scored above the threshold enabled us to collect and analyze parental concerns and stressors that were occurring at those time points.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

One of the aims of The BabySeq Project was to examine the psychological impact of exome sequencing on parents of sick and well infants [see Holm, et. al, for a full description (Holm et al., 2018)]. In brief, parents and newborns from the well-baby nursery at Brigham and Women's Hospital (BWH) and parents and sick newborns from the neonatal intensive care unit and other intensive care units (NICU/ICUs) at BWH, Boston Children's Hospital (BCH), and Massachusetts General Hospital (MGH), were approached, consented, and enrolled into the study. Both parents were consented and enrolled, if known, however single parent families were eligible to participate if the other biological parent was not known (i.e. Anonymous sperm donor). A blood sample was obtained from the newborn for analysis whereas parents provided saliva samples. Within each cohort, healthy and sick, the families were randomized to a modified standard of care - family history and standard newborn screening (NBS) [the control arm] - or to the modified standard of care plus exome sequencing (ES) [the ES arm]. Both arms had a three-generation family history collected and evaluated by a study genetic counselor. Additionally, parental surveys at enrollment (baseline), immediately post-disclosure, and 3 months post-disclosure were conducted, which included psychosocial measurements to determine whether there were changes in depression and/or anxiety after sequencing results were returned (see Appendices 1 and 2). The BabySeq Project implemented a safety protocol that included outreach by the study psychologist if a parent scored above a designated threshold on the depression and/or anxiety screening measure(s), allowing for a full screening and documentation of parental concerns to determine whether they were related to sequencing results or parenting stress.

The ES data in newborns randomized to the ES arm were analyzed to identify 'monogenic disease risk', that is, pathogenic or likely pathogenic variants in genes for childhood-onset conditions (about 1,000) and two highly actionable adult-onset conditions, Lynch syndrome and Hereditary Breast and Ovarian syndrome. Carrier status was also assessed (Ceyhan-Birsoy et al., 2017), and these results were returned to the parents. Parents were only tested for a variant if it would aid in interpreting the variant in the infant; carrier status was not confirmed in the parents. Parents attended a

disclosure session, on average four months after enrollment (range: 1.2 to 10.2 months), where they were informed of their randomization status, given their family history report, and if they were in the ES arm, given the genomic results. Parents provided consent for their and their child's participation in the study, including all communication with study staff, and Institutional Review Boards (IRB) at Partners HealthCare (now Mass General Brigham), BCH, and the Baylor College of Medicine approved this study.

2.2 | Data collection

2.2.1 | Edinburgh postnatal depression scale data

Screening for Major Depressive Disorder with Peripartum Onset was assessed using the Edinburgh Postnatal Depression Scale (EPDS) at three time points: baseline, immediately post-disclosure of results, and 3 months post-disclosure of results (see Appendix 1). The EPDS is a depression screening tool that is widely used clinically in postpartum mothers and fathers (Carlberg et al., 2018; Chiu et al., 2017; Cox et al., 1987; Matthey & Agostini, 2017; Rafferty et al., 2019; Stewart & Vigod, 2016; Wilkinson et al., 2017). The scale has 10 items with response options scored from 0–3, with high scores indicating greater symptom severity. The total score ranging from 0 to 30 is calculated by tallying the responses from each item (Cox et al., 1987). We designated a score of 12 or above for mothers and 10 or above for fathers as the thresholds for clinical concern for Major Depressive Disorder with Peripartum Onset, based on thresholds used in other studies (Carlberg et al., 2018; Cox, 2019; Cox et al., 1987; Matthey & Agostini, 2017).

2.2.2 | Parent conversation data

The safety protocol for the study included a genetic counselor reviewing the EPDS responses of parents who scored at or above thresholds for clinical concern on the EPDS at any time point. All parents who scored at or above the threshold for clinical concern for the first time were contacted by the study psychologist (SEW) or, if she was unavailable, by the study genetic counselor who was trained in mental health counseling. If the parent of an infant in the NICU maintained his/her relationship with the NICU social work team, the study genetic counselor reached out to the social worker who contacted the parent. The purpose of this contact was to determine if parents were in need of mental health counseling or emergency intervention. The psychologist, genetic counselor, or social worker prefaced the follow-up contact with: 'My role is to follow up with families who are participating to ensure that the study is not causing undue stress and that parents are feeling OK. Recently, some of your responses suggested that you are having some upsetting feelings and I want to be sure that you have the support that might be helpful to you' (see full script in Supporting Information). All phone discussions with the parent were documented but they were not recorded nor transcribed. If the parent did not answer the phone, a message was left explaining the reason for the call, and a follow-up email (see Supporting Information) was sent to the parent with study contact information. Documentation of phone calls and the responses to emails were collected by the study research assistant (TSS). If a parent also scored high on subsequent EPDS', the study psychologist determined whether additional contact should be made or if it was not necessary because either the parent was referred to an outside therapist during the initial safety check in and now indicated that they were in counseling or they were still being followed by their inpatient social worker.

2.3 | Data analysis

2.3.1 | EPDS

To understand whether elevated scores on depression scales persisted over time, quantitative analyses included participants who scored above thresholds for clinical concern on the EPDS at any time point it was administered. To examine whether participants who scored above the threshold for depression at baseline differed by demographic characteristics from participants who scored above thresholds at post-disclosure time points, we used chi-squared and *t* tests. We also used these statistical approaches to compare parents who provided data for qualitative analyses versus those who did not.

To examine the trajectories of parents who scored at or above the threshold for clinical concern, we used generalized linear models fit with generalized estimating equations in longitudinal analyses that examined changes from baseline on the EPDS. Separate models were run for parents who scored above thresholds on the EPDS at baseline, below thresholds at baseline but above them in the post-disclosure survey, and above thresholds on only the 3-month post-disclosure survey. Given the limited number of parents who scored above the threshold for concern, statistical models included only the variables of interest (e.g., randomization status and survey time point) as covariates. Models that tested the impact of learning about an unexpected monogenic disease risk were limited to data from the ES arm. Missing data were imputed using the last observation carried forward or the next observation carried backwards if baseline data were unavailable.

2.3.2 | Parent conversation

Notes documenting study staff contacts with parents were coded using thematic content analysis by two coders (TSS and MKU) who were not involved in communicating with parents. One coder (TSS) read through the notes to develop a preliminary codebook of themes and definitions capturing influencers of parents' EPDS scores. To ensure rigor and reliability, both coders then used these preliminary themes to independently code the responses from nine randomly selected parent conversations. Coders then met to discuss and

resolve coding discrepancies using consensus and finalize themes/sub-themes and their definitions. The final codebook, including three themes and seven sub-themes, was used by both coders to independently code the remaining parent conversations. Coders met to discuss each parent conversation and resolve coding discrepancies through consensus. Notes or responses representing more than one theme/sub-theme were coded for each theme/sub-theme characterized. Additionally, sub-theme frequencies were calculated by counting the sub-theme once if it was reported by a parent, regardless of how many times the sub-theme was mentioned in the parents' response.

3 | RESULTS

3.1 | Participant characteristics

Of the BabySeq parents who provided depression data within the baseline survey ($n = 527$), 45 scored at or above thresholds for clinical concern on the EPDS (Table 1). Parents were more likely to score high at baseline if their newborn was in the sick cohort than the well-baby cohort (OR = 3.5, 95%CI: 1.8 to 7.0, $p < .001$), and mothers were more likely to score higher than fathers (OR = 2.1, 95%CI: 1.0 to 4.3, $p = .041$). There was no difference between study arms, demographic, or study characteristics for parents scoring above versus below thresholds for concern. Eleven of the 45 parents did not complete the EPDS at either the immediate or 3-month post-disclosure time points and six others completed the EPDS at the immediate but not the 3-month post-disclosure time point (see Appendix 3). As previously described in regard to the overall study population (Pereira et al., 2019), parents who scored above thresholds at baseline were predominantly White, similarly well educated (86.7% with a bachelor's degree or higher) and had household incomes at or above $100,000 (76.7%). Nearly half of the parents who scored above thresholds on the EPDS at baseline (20 of 45; 44.4%) reported that the newborn enrolled in The BabySeq Project was their first child.

Twenty-eight parents scored below the threshold for clinical concern at baseline but scored at or above the threshold on the EPDS within the immediate post-disclosure survey. Compared to parents who scored high at baseline, parents who did not score high at baseline but first scored high at the immediate post-disclosure time point were more likely to be fathers (33.3% versus 60.7%, respectively, $p = .020$) and in the well-baby cohort (53.3% versus 85.7%, respectively, $p = .010$). No differences in demographic or study-related characteristics were observed between parents who scored high at immediate post-disclosure compared to parents who did not at baseline or immediate post-disclosure (all $p > .10$). Five of these parents had not completed the baseline EPDS, and another seven did not complete the EPDS at 3 months post-disclosure (see Appendix 3). Nine parents scored above the threshold on the EPDS only at the 3-month post-disclosure time point. No differences in demographic or study-related characteristics were observed between parents who scored high on the EPDS only at 3 months post-disclosure compared to parents who scored high at baseline (all $p > .20$). Two of these parents had not completed the baseline EPDS, and another did not complete the EPDS on the immediate post-disclosure survey.

Characteristics of the 43 parents who provided data for qualitative analyses during their safety screens are summarized in Table 1. Twenty-six of these 43 parents scored high at baseline: 16 spoke with the study psychologist on the phone, seven interacted with study staff via email, and three met with study staff or a social worker in person. The other seventeen parents scored high only at one of the two post-disclosure time points (immediately or 3 months post-disclosure): 11 spoke with the study psychologist on the phone, five interacted with study staff via email, and one interacted with study staff in person. No differences in demographics were observed between parents included in quantitative versus qualitative analyses.

3.2 | EPDS results

Of the 34 parents who had depression scores at or above the threshold for clinical concern at baseline and provided EPDS data on the immediately or 3-month post-disclosure surveys, the depression scores for 25 parents (73.5%) decreased on a subsequent post-disclosure survey. Figure 1 shows that for parents who completed the EPDS at baseline and the immediate or 3-month post-disclosure time points, EPDS scores were, on average, 2.9 points lower at the immediate post-disclosure time point compared to baseline (95%CI: −4.2 to −1.6, $p < .001$); and 1.1 points lower at 3 months post-disclosure, on average, than immediately post-disclosure (95%CI: −2.0 to −0.2, $p = .014$). Analyses examining whether time-averaged changes from baseline differed by experimental, study, or participant characteristics found no differences between randomization arms ($p = .339$), birth mothers versus fathers ($p = .649$), or newborn cohorts ($p = .298$). We also observed no differences between parents who spoke to the study team or to the NICU social worker ($p = .696$). Sub-analyses of the 25 parents in the ES arm showed no differences in time-averaged change scores between the three parents of newborns identified with an unexpected monogenic disease risk and the 22 parents of newborns with no unexpected monogenic disease risk (−5.8 versus −3.9, respectively, $p = .328$).

Figure 2 illustrates the mean EPDS depression scores of parents who scored at or above the threshold for clinical concern starting at the immediate post-disclosure time point. On average, EPDS scores increased by 4.7 points from baseline to immediately post-disclosure among these parents (95% CI: 3.4 to 5.9, $p < .001$), but decreased by 3.8 points at the 3-month post-disclosure time point (95% CI: 2.6 to 5.0, $p < .001$). No personal or study-related characteristics were found to be associated with changes in EPDS scores, including disclosure of an unexpected monogenic disease risk. The difference in mean change in EPDS scores from baseline to immediately post-disclosure was +3.7 among the three parents whose child had an unexpected monogenic disease risk and +4.4 among the 25 parents whose child did not ($p = .671$); the difference in mean change in EPDS scores from immediately post-disclosure to 3 months post-disclosure

TABLE 1 Characteristics of The BabySeq Project participants who scored above the clinical threshold for concern for depression on the Edinburgh Postnatal Depression Scale, stratified by randomization status

	High at baseline		Below threshold at baseline but high post-disclosure		High only at 3 months post-disclosure		Spoke with study staff	
Characteristic	Control arm (*n* = 20)	ES arm (*n* = 25)	Control arm (*n* = 13)	ES arm (*n* = 15)	Control arm (*n* = 2)	ES arm (*n* = 7)	Control arm (*n* = 19)	ES arm (*n* = 24)
Parent, *n* (%)								
Birth mother	13 (65.0%)	17 (68.0%)	5 (38.5%)	6 (40.0%)	2 (100.0%)	5 (71.4%)	12 (63.2%)	14 (58.3%)
Father	7 (35.0%)	8 (32.0%)	8 (61.5%)	9 (60.0%)	0 (0.0%)	2 (28.6%)	7 (36.8%)	10 (41.7%)
Cohort, *n* (%)								
Well baby	12 (60.0%)	12 (48.0%)	10 (76.9%)	14 (93.3%)	1 (50.0%)	4 (57.1%)	11 (57.9%)	15 (62.5%)
Sick baby	8 (40.0%)	13 (52.0%)	3 (23.1%)	1 (6.7%)	1 (50.0%)	3 (42.9%)	8 (42.1%)	9 (37.5%)
Race, *n* (%)								
White	13 (65.0%)	18 (72.0%)	10 (76.9%)	11 (73.3%)	0 (0.0%)	5 (71.4%)	12 (63.2%)	17 (70.8%)
Other/more than one race	5 (25.0%)	6 (24.0%)	2 (15.4%)	2 (13.3%)	2 (100.0%)	2 (28.6%)	5 (26.3%)	4 (16.7%)
Not available	2 (10.0%)	1 (4.0%)	1 (7.7%)	2 (13.3%)	0 (0%)	0 (0%)	2 (10.5%)	3 (12.5%)
Age, mean years (sd)	35.4 (5.4)	35.1 (3.4)	35.4 (5.6)	35.0 (6.8)	36.2 (5.5)	36.4 (5.1)	35.9 (5.3)	34.8 (4.9)
Not available, *n* (%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	4 (26.7%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	2 (8.3%)
Median household income	$100–199K	$100–149K	$100–199K	$200–499K	$100–199K	$200–499K	$100–199K	$200–499K
Not available, *n* (%)	2 (10.0%)	0 (0.0%)	1 (7.7%)	1 (6.7%)	0 (0.0%)	2 (28.6%)	1 (5.3%)	2 (8.3%)
Bachelor's degree or higher, *n* (%)	19 (95.0%)	20 (80.0%)	11 (84.6%)	14 (100.0%)	2 (100.0%)	6 (85.7%)	18 (94.7%)	21 (87.5%)
Not available, *n* (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (4.2%)
First child, *n* (%)	13 (65.0%)*	7 (28.0%)*	8 (66.7%)	6 (40.0%)	0 (0.0%)	4 (57.1%)	10 (52.6%)*	5 (20.8%)*
Not available, *n* (%)	1 (5.0%)	1 (4.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (10.5%)	1 (4.2%)
Baseline EPDS score, mean (*SD*)	13.4 (2.4)	13.7 (2.2)	7.1 (4.1)	8.4 (3.0)	6.5 (0.7)	6.2 (1.8)	10.9 (4.7)	11.7 (3.4)
Not available, *n* (%)	0 (0%)	0 (0%)	1 (7.7%)	4 (26.7%)	0 (0%)	2 (28.6%)	0 (0%)	2 (8.3%)

*Differences between randomization arms at $p < .05$.

was −5.3 among parents whose child had an unexpected monogenic disease risk and −2.6 among parents whose child did not ($p = .191$).

Figure 3 illustrates the mean EPDS depression scores of parents who scored at or above the threshold for clinical concern only at the 3-month post-disclosure time point. On average, EPDS scores increased by 1.0 point from baseline to immediately post-disclosure among these parents (95% CI: −0.8 to 2.8, $p = .275$) and increased an additional 5.7 points at the 3-month post-disclosure time point (95% CI: 3.5 to 7.8, $p < .001$). Increases were 2.7 points greater among the two participants in the control arm compared to the ES arm (95% CI: 0.3 to 4.6, $p = .024$), and 4.6 points greater among mothers than fathers (95% CI: 2.3 to 6.9, $p < .001$). No other personal or study-related characteristics were found to be associated with changes in EPDS scores.

3.3 | Parent conversation results

Among the 82 parents who scored at or above the threshold for clinical concern on the EPDS, 43 (52.4%) provided information for qualitative analyses, 7 (8.54%) of whom were contacted more than once because of elevated scores at multiple time points. In general, parents appreciated the outreach by the study staff and were comfortable discussing their feelings. A total of 50 encounters were

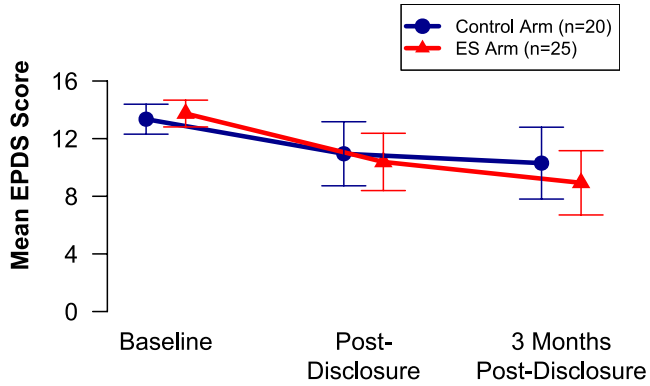

FIGURE 1 Mean depression scores and 95% confidence intervals of parents who scored above the clinical threshold for concern on the Edinburgh Postnatal Depression Scale at baseline, stratified by randomization status

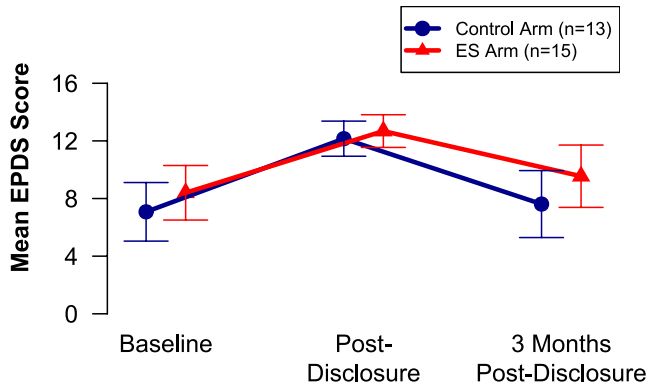

FIGURE 2 Mean depression scores and 95% confidence intervals of parents who scored below the clinical threshold for concern on the Edinburgh Postnatal Depression Scale prior to disclosure of results and above the clinical threshold for concern at the immediate post-disclosure time point, stratified by randomization status

coded from 43 parents that yielded three main categories of themes: stressors or concerns, coping response, and response to research (see Table 2).

3.3.1 | Stressors or concerns

Three sub-themes addressed stressors that parents were experiencing over the course of the study: parenting-specific stress, work/family/life stress, and child health concerns.

Parenting-specific stress

One quarter (25.6%, $n = 11$) of parents mentioned parenting-specific stress contributing to their depressive symptoms. Four parents attributed this stress to the overwhelming adjustment of being a first-time parent. Some parents described how expanding their family, for example, now having two children, was the source of their increased stress.

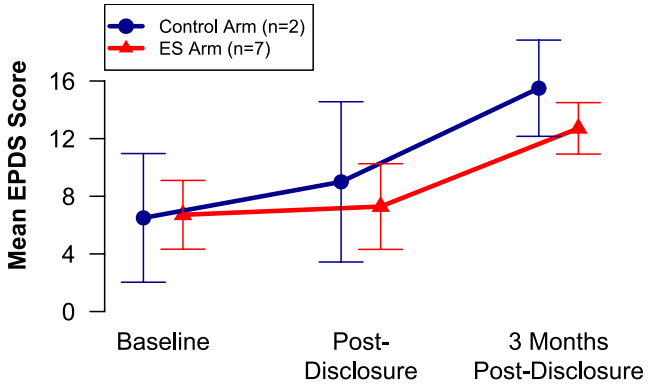

FIGURE 3 Mean depression scores and 95% confidence intervals of parents who scored above the clinical threshold for concern on the Edinburgh Postnatal Depression Scale only at the 3-month post-disclosure time point, stratified by randomization status

Work, family, life stress

Similarly, one quarter (25.6%, $n = 11$) of parents described the stress of balancing the needs of their newborn with other work, family, or life stresses. For some, going back to work and trying to balance their already-stressful job with a newborn proved challenging. Other parents described events that caused added stress. For instance, one father attributed his depression to the hospitalization of a family member. Similarly, two mothers, one of whom was readmitted to the hospital over the course of the study, noted that their own medical status added to their stress during the time of survey completion, thus impacting their responses.

Child health concerns

Slightly less than one-fifth (18.6%, $n = 8$) of parents described the stress of their child's health as contributing to their depressive symptoms, such as the acute decompensation of their newborn. Other parents struggled with ongoing concern over chronic health issues for their child. For example, one mother described feelings of disappointment that it might be months before her son's nasogastric tube could be removed.

3.3.2 | Coping

A number of parents were either utilizing coping support during study participation or coordinating support for future use. Thirty percent ($n = 13$) of parents cited specific supports they had received or considered using because of feeling overwhelmed for reasons unrelated to study participation. Four parents had accessed mental health counseling and three were considering counseling for depressive symptomatology; two of these parents had started, and one was considering, antidepressant medications. Six parents indicated that their family or community had provided emotional and/or practical support. Another mother stated that the social workers in the NICU

TABLE 2 Themes reported by parents following elevated Edinburgh Postnatal Depression Scale scores

			Parents Reporting ($n = 43$)	
Theme ($n = 3$)	**Sub-Theme ($n = 7$)**	**Definition**	**No.**	**%**
Stressors or Concerns	Parenting-specific Stress	Demands of first-time parenting, or balancing two or more children, caused parent mental or emotional distress	11	25.6
	Work, Family, Life Stress	Demanding circumstances in parent's work, family, or life causing mental or emotional strain	11	25.6
	Child Health Concerns	Ongoing hospitalization or continuing symptoms after discharge caused parent worry	8	18.6
Coping Response	Support Parents Sought	Assistance parents sought to manage stress	13	30.2
Response to Research	Research Concerns	Study logistics (i.e. randomization) caused parent worry or upset	3	7.0
	No Research Concerns	Parent expressed no worry, strain, or upset over participating in the research study	17	39.5
	Positive Research Experience	Parent expressed a positive response or appreciation related to being involved in the research study	12	27.9

had met with her and were helpful. Two mothers requested ongoing contact with the study psychologist as a means of support.

3.3.3 | Response to research

The last set of sub-themes describe parents' response to participating in The BabySeq Project and how participation contributed to or alleviated their stress: research concerns, no research concerns, and positive research experience.

Research concerns

Only one parent described genomic sequencing of his newborn as counterproductive since receiving a negative genetic report would confirm what the parent already thought (that the child was healthy), and receiving a positive genetic finding would be upsetting. Nevertheless, this parent was still glad to participate in the study. Two parents expressed disappointment that their child was not randomized into the sequencing arm. No parents cited return of genomic results as contributing to their elevated stress.

No research concerns

Forty percent ($n = 17$) of parents explicitly stated that participation in our study did not cause stress or concern. One mother stated that she had not thought about the study beyond filling out the questionnaires, given the other concerns she was facing with her newborn and other children at home.

Positive research experience

Over a quarter of parents (27.9%, $n = 12$) emphasized the positive impact of participating in the study. Most found participation interesting or enjoyable, while others felt empowered and glad to contribute to research for altruistic reasons.

4 | DISCUSSION

Our analysis of data obtained from The BabySeq Project failed to show a significant effect of parental participation in a newborn genomic sequencing study, as evidenced by the incidence and severity of postpartum parental depression. Over the course of the first months of the study, parents in both the sequencing and control arms exhibited similar, transient elevations of EPDS scores. Receipt of sequencing results did not contribute to the elevated EPDS scores, rather most parents attributed elevated scores to parenting concerns or worries about work–life balance or their child's health.

It is typical for new parents to be concerned about the growth, development, and health status of their infant (Entsieh & Hallström, 2016; Wiklund et al., 2018). In our study, these concerns appeared to be particularly salient among parents with newborns in the NICU/ICU cohort, who often had health issues that were unresolved at the time parents completed surveys. In addition, work/life/general stressors were common at the immediate and 3-month post-disclosure time points, when parents were beginning to return to work and adjusting to new routines. Child health concerns were another poignant theme in our parents' responses, and commonly exacerbated parental stress during the newborn period. We chose to only code responses in which parents made negative comments about their child's health, since we were examining parental concerns, but many parents noted their child's positive health status during discussions.

Our findings also highlight the importance of considering context when drafting protocols to ensure the safety of participants in genomic research. Based on our findings, an argument could be made that the rigorous and time-intensive safety protocol with respect to parental depression or anxiety screening that we implemented in the research setting may not be necessary. According to best practice clinical recommendations, parents should be receiving

the same depression screening that we conducted prior to postpartum hospital discharge and at subsequent obstetrics and pediatrics visits ('ACOG Committee Opinion No. 757: Screening for Perinatal Depression', 2018; Earls et al., 2019). When indicated, parents should be referred to mental health services (Stewart & Vigod, 2016). Our baseline survey, which included the EPDS, should have overlapped with clinical surveillance, and thus parents should have received appropriate mental health referrals regardless of our monitoring and intervention. Although we believe it is important to capture baseline depression and anxiety levels in the research setting, since a significant change in scores at post-disclosure would only be captured by having a baseline data point, a rigorous safety protocol may not be needed as depression screening follow-up is implemented in the clinical setting. On the other hand, while the clinical team will intervene at the baseline time point if the parent's depression and anxiety score is elevated, it is the researchers' responsibility to re-assess parents at post-disclosure time points for significant changes in depression and anxiety and make the appropriate mental health referrals.

It should be noted that while psychological screening is common in genomics research, clinical genomic testing providers do not screen for depression or anxiety after return of results, primary or secondary (Levy et al., 2019; Orlando et al., 2018; Weitzel et al., 2016). Additionally, direct-to-consumer genomic testing, which is now available for infants and children, has no follow-up counseling after results are returned, let alone psychological screening. A potential area to study would be to evaluate if there are increased rates of depression and/or anxiety, especially with the return of secondary findings in the clinical realm, as well as in direct-to-consumer testing.

The BabySeq Project is unique in that parents were screened for depression and anxiety at baseline, and even if the parent had an elevated score and could be considered 'vulnerable', they were still allowed to participate. In studies such as REVEAL and MedSeq, participants who scored above the threshold for clinical concern were excluded (Christensen et al., 2016, 2020; Green et al., 2015; Vassy et al., 2014). Offering enrollment in studies of genomic screening to all individuals, regardless of baseline depression and anxiety status, is potentially very informative since the purpose of these studies is to inform future genomic sequencing in the clinical setting, which will include individuals with depression and anxiety. In addition, future standard newborn screening may shift to include sequencing, and thus all parents will have the potential to receive information about monogenic risk for diseases, such as the secondary findings recommended by the American College of Medical Genetics and Genomics (Kalia et al., 2017), including the 10%–15% of mothers and 8%–10% of fathers in the general population who have postpartum depression (Carlberg et al., 2018; Matthey & Agostini, 2017; Scarff, 2019). Therefore, it is important for research assessing the impact of integrating sequencing into newborn screening to include all parents, whether or not they screen high for depression and anxiety at baseline, and to follow-up with these parents in order to understand the potential implications on a population basis.

An important limitation of this study was selection bias. The majority of parents were White, well-educated, and had a household income of >$100,000/year (Pereira et al., 2019). These results may not be generalizable to parents with lower income or lower educational achievements and it will be important to expand the economic, educational, and racial diversity of populations studied to better understand the potential psychological effects of newborn genomic sequencing across a much broader population. Furthermore, the study's time commitment was such that severely clinically depressed parents may not have enrolled and this may also have limited enrollment from households with lower income levels. Future studies are in development to address these limitations by targeting enrollment to underrepresented minorities and families of lower socioeconomic status. Another limitation is that we were only able to contact 52.4% of the parents with elevated scores.

In conclusion, while many studies have shown little psychological impact from disclosing genetic risk information (Bloss et al., 2013; Christensen et al., 2016; Hartz et al., 2014; Heshka et al., 2008; Robinson et al., 2019), questions have persisted about its safety among individuals who are already experiencing distress before undergoing genetic testing (Gray et al., 2014). Importantly, we demonstrate that participation in a randomized-controlled study of ES in newborns, which included the return of results in the sequencing arm, did not raise significant concerns for parents in our study. Rather, our findings reiterate what every parent knows: having a newborn is challenging, especially if the baby is in the NICU, but also if the baby is well, and adding a newborn to a family with other children increases parental stress.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work and/or the acquisition, analysis, or interpretation of data for the work. All authors aided in drafting the work or revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST

RCG has received compensation for advising the following companies: AIA, Grail, Plumcare, UnitedHealth, Verily, VibrentHealth, Wamberg; and is co-founder of Genome Medical, Inc. All other authors declare no conflict of interest.

HUMAN STUDIES AND INFORMED CONSENT

Approval to conduct this human subjects research was obtained by the Institutional Review Boards at Partner's Healthcare, BCH, and

the Baylor College of Medicine. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants included in the study.

ANIMAL STUDIES

No non-human animal studies were carried out by the authors for this article.

DATA SHARING AND DATA ACCESSIBILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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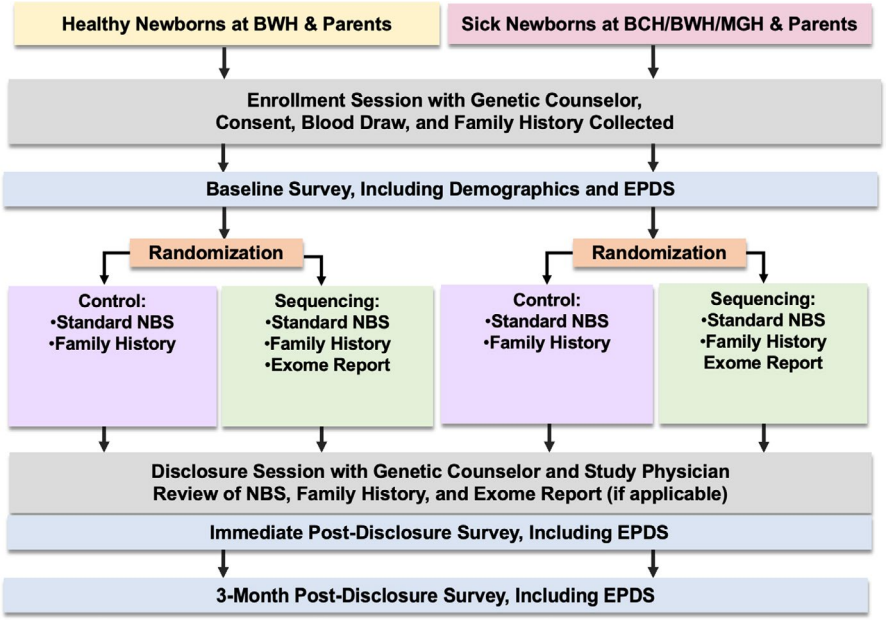
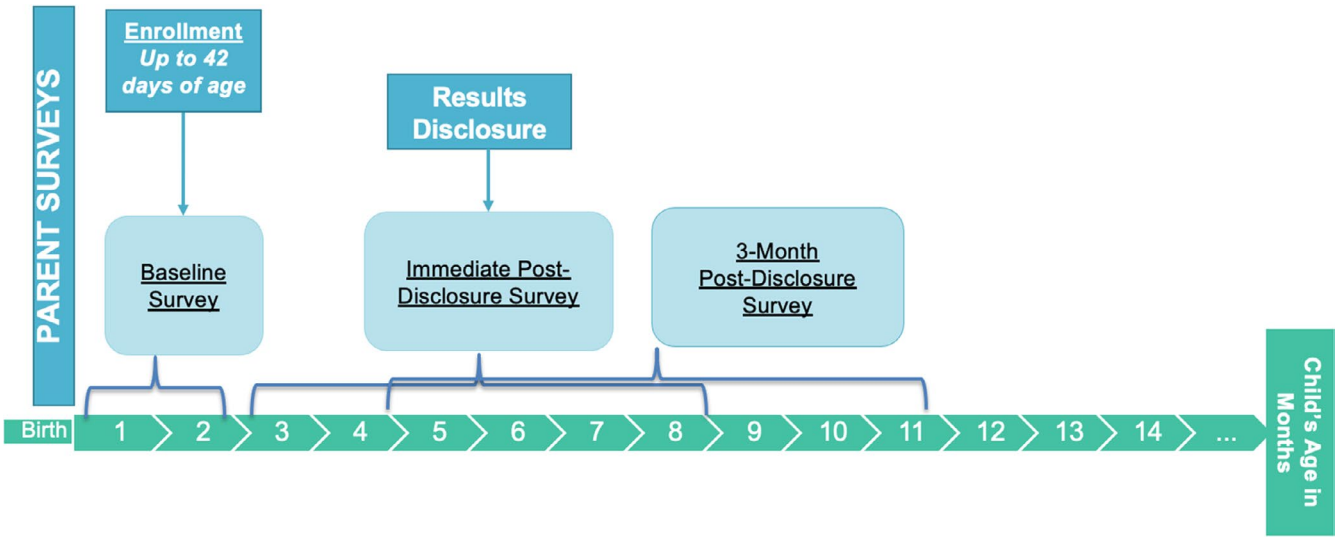
APPENDIX 1.

Flow diagram of The BabySeq Project protocol. BWH, Brigham and Women's Hospital; BCH, Boston Children's Hospital; MGH, Massachusetts General Hospital; EPDS, Edinburgh Postnatal Depression Scale; NBS, Newborn Screening.



APPENDIX 2.

Timeline of parental surveys in relation to child's age in months. For the baseline survey, average age of the child was 0.5 months with a range of 0.1–1.7 months. Mean age of the child for the immediate post-disclosure survey was 5.3 months, with a range of 2.3–12.7 months. There was one outlier not shown in the brackets in which the immediate post-disclosure survey was not completed until the child was 12.7 months (shown range is 2.3–9.0, which excludes the outlier). For the 3-month post-disclosure survey, average age of the child was 8.3 months, with a range of 5.0–11.8 months.



APPENDIX 3.

Study consort diagram of participants included in analyses.